Claims

What Is Claimed Is:

1. A method of producing a folded extramembranous receptor domain of a membrane protein receptor, said method comprising:

forming a chemical ligation product comprising an extramembranous receptor domain of a selected membrane protein receptor by ligating under chemoselective chemical ligation conditions first and second peptides of said extramembranous receptor domain, said peptides having compatible unprotected chemoselective reactive groups capable of forming a covalent bond therein between;

exposing said chemical ligation product to a folding buffer having a buffering reagent, a chaotropic reagent and an organic solvent that mimics the water-lipid interface environment of a cell membrane; and

isolating from said folding buffer chemical ligation product that binds to a ligand of said extramembranous receptor domain of said membrane protein receptor, whereby a folded extramembranous receptor domain of a membrane protein receptor is produced.

2. The method of Claim1 wherein said extramembranous receptor domain is an extracellular domain.

3. The method of Claim 2 wherein said extracellular domain is an amino terminal domain.

4. The method of Claim 2 wherein said extramembranous receptor domain is derived from a receptor selected from the group consisting of a G-protein coupled receptor and an enzyme-linked protein receptor.

5. The method of Claim 4 wherein said G-protein coupled receptor is a type B G-protein coupled receptor.

6. The method of Claim 5 wherein said type B G-protein coupled receptor is glucagon-like peptide 1 receptor.

7. The method of Claim1 wherein said chemical ligation is selected from the group consisting of native chemical ligation, oxime-forming ligation, thioester-forming ligation, thioether-forming ligation, hydrazone-forming ligation, thiazolidine-forming ligation, and oxazolidine-forming ligation.

8. The method of Claim 1 wherein said organic solvent is a water soluble organic solvent.

9. The method of Claim 8 wherein said water soluble organic solvent is methanol.

10. The method of Claim 1 wherein said first peptide comprises an unnatural amino acid.

11. The method of Claim 10 wherein said unnatural amino acid comprises a chemical moiety selected from the group consisting of a chromophore and a hapten.

12. The method of Claim 11 wherein said chromophore is a fluorophore.

13. The method of Claim 11 wherein said hapten comprises a biotin moiety.

14. A composition comprising a chemically synthesized extramembranous receptor domain produced according to the method of Claim 1.

15. A kit comprising a composition according to Claim 14.

16. A composition comprising a synthetic extramembranous receptor domain of a membrane protein receptor having a chemically synthesized segment that includes an unnatural amino acid at a pre-selected residue position, wherein said extramembranous receptor domain is free of a membrane spanning transmembrane domain and is capable of binding to a ligand of said membrane protein receptor.

17. The composition of Claim 16 wherein said composition is completely free of cellular contaminants.

18. The composition of Claim 16 wherein said unnatural amino acid comprises a chemical moiety selected from the group consisting of a chromophore and a hapten.

19. The composition of Claim 18 wherein said chromophore is a fluorophore.

20. The composition of Claim 18 wherein said hapten comprises a biotin moiety.

21. The composition of Claim 16 wherein said synthetic extramembranous receptor domain is attached to a support matrix.

22. The composition of Claim 21 wherein said support matrix is a MALDI slide.

23. The composition of Claim 21 wherein said support matrix is a polymer.

24. A method of assaying a soluble extramembranous receptor domain for ligand-induced dimerization, said method comprising:

contacting a soluble extramembranous receptor domain of a membrane protein receptor with a ligand of said membrane protein, wherein said soluble extramembranous receptor domain is free of a membrane spanning transmembrane domain; and

assaying said soluble extramembranous receptor domain for ligand-induced dimerization.

25. The method of Claim 24 wherein said soluble extramembranous receptor domain comprises an unnatural amino acid.

26. The method of Claim 25 wherein said unnatural amino acid comprises a chemical moiety selected from the group consisting of a chromophore and a hapten.

27. The method of Claim 26 wherein said chromophore is a fluorophore.

28. The method of Claim 26 wherein said hapten comprises a biotin moiety.

29. The method of Claim 24 wherein said extramembranous receptor domain is attached to a support matrix.

30. The method of Claim 25 wherein said assaying is characterized by detection of a property of said unnatural amino acid.

31. The method of Claim 30 wherein said unnatural amino acid comprises a chromophore and said property is fluorescence.

32. The method of Claim 24 wherein said ligand comprises a detectable label.

33. The method of Claim 32 wherein said detectable label is a chromophore.

34. The method of Claim 24 wherein said assaying is characterized by detection of a property of said ligand.

35. The method of Claim 34 wherein said ligand comprises a chromophore and said property is fluorescence.

36. A method of detecting binding of a ligand to an extramembranous receptor domain of a membrane protein receptor, said method comprising:

contacting a soluble extramembranous receptor domain of a membrane protein receptor with a ligand of said membrane protein receptor, wherein said soluble extramembranous receptor domain is free of a membrane spanning transmembrane domain and comprises an unnatural amino acid having a detectable moiety; and

assaying said soluble extramembranous receptor domain for ligand-induced dimerization of monomers of said extramembranous receptor domain.

37. The method of Claim 36 wherein said ligand is selected from the group consisting of agonist and antagonist.

38. The method of Claim 37 wherein said antagonist is a partial antagonist.

39. The method of Claim 37 wherein said agonist is a partial agonist.

40. The method of Claim 36 wherein said extramembranous receptor domain is an extracellular domain.

41. A method of detecting binding of a ligand to an extramembranous receptor domain of a membrane protein receptor, said method comprising:

contacting a soluble extramembranous receptor domain of a membrane protein receptor with a ligand for said membrane protein receptor, wherein said soluble extramembranous receptor domain is free of a membrane spanning transmembrane domain and comprises an unnatural amino acid having a detectable moiety; and

detecting binding of said ligand to said soluble extramembranous receptor domain by assaying for a change in a property of said detectable moiety.

42. The method of Claim 41 wherein said detectable moiety is a chromophore and said property is energy transfer.

43. The method of Claim 41 wherein said ligand is selected from the group consisting of agonist and antagonist.

44. The method of Claim 43 wherein said antagonist is a partial antagonist.

45. The method of Claim 43 wherein said agonist is a partial agonist.

46. The method of Claim 41 wherein said soluble extramembranous receptor domain is an extracellular domain.